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# Bladder PDT With Intravesical Clear and Light Scattering Media: Effect of an Eccentric Isotropic Light Source on the Light Distribution

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***Background and Objective:*** **Whole bladder wall photodynamic therapy (PDT) is sometimes performed with a light scattering medium in the bladder, as it is assumed that this will promote a more uniform illumination of the bladder wall. The influence of eccentric placement of an isotropic light emitting diffuser on the homogeneity of the light distribution at the bladder wall is assessed.**

***Study Design/Materials and Methods:*** **Whole bladder wall irradiations were performed at ≈630 nm, and fluence rates were measured with and without controlled amounts of Intralipid® in an ex vivo pig bladder and in vitro in a bladder phantom. Experimental values were compared to Monte Carlo simulations using in vitro bladder optical properties.**

***Results:*** **An eccentric diffuser in a clear intravesical medium produces a better uniform illumination than in a light scattering intravesical medium. Also, intravesical light absorption, e.g., by urine, would lead to a substantial loss of the energy delivered in case of light scattering cavity contents.**

***Conclusion:*** **The use of a clear intravesical medium guarantees the highest and most uniform fluence rate at the bladder wall during optical irradiation with an isotropic light source in clinical PDT of nonspherical bladders, whereas an intravesical light scattering medium reduces both the magnitude and the uniformity of the fluence rate. Lasers Surg. Medicine 20:248–253, 1997.**



**Key words: bladder phantom; Monte Carlo simulations; photodynamic therapy; tissue optics**

## INTRODUCTION

Optical irradiation of the bladder in photodynamic therapy (PDT) is most often performed using an isotropic light source centered in the bladder cavity. This whole bladder wall (WBW) therapy ensures the complete treatment of diffuse, visible and invisible, superficial carcinoma [1–4]. During the optical irradiation, the bladder cavity (or a balloon within) is usually filled with clear saline to unfold the bladder wall, but sometimes a light scattering medium is used [5]. The latter is assumed to promote a more uniform light distribution at the bladder wall, which thus would prevent under or over dosage of the light at certain spots and is predicted to be more efficient inside the tissue [6]. This report assesses the influence of eccentric positioning of the light emit-

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ting diffuser on the homogeneity of the light distribution at the bladder wall.

Experiments were performed using light of ≈630 nm wavelength with and without controlled amounts of Intralipid® in an ex vivo pig bladder and in a bladder phantom. Experiments were also simulated with the computer using bladder optical properties determined in vitro, which gives detailed information on the optical penetration in the bladder wall.

## MATERIALS AND METHODS

Ex vivo experiments were performed on one bladder, which was removed from a pig of 27 kg. The bladder tissue did not contain any photosensitizer. The bladder was placed at the center of a transparent plastic sphere (diameter 13.5 cm, volume 1250 ml) filled with saline (Fig. 1). Irradiations were performed with 630 nm light from an $Ar^+$-dye laser and using a modified cystoscope [7] as described previously [8, 9]. During a WBW irradiation, the light fluence rate ($\Phi$) was kept low and was simultaneously recorded at three positions on the bladder wall halfway into the bladder cavity. If the isotropic light source (isotropy < ±15%) was positioned in the center of the bladder cavity, the deviations from the mean fluence rate at the bladder wall were always <10% across the whole bladder surface. The light fluence multiplication factor ($\beta$) of this bladder was 5.2(3). (Numbers in parentheses are the standard deviation uncertainties in the last digit(s) of each quoted value: = standard error of the mean.) Here, $\beta = \Phi/\Phi_{nsl}$, where $\Phi_{nsl}$ is the nonscattered optical irradiance. The integrating sphere effect [10] in the ex vivo pig bladder is within 10% of the mean value encountered in clinical practice [1, 3]. Calibration of the three isotropic light detectors (isotropy < ±20%) and the output power of the diffuser was checked before and after the measurements (deviations <3% and <5%, respectively) [11]. First, the bladder cavity was filled with 150(5) ml of saline. The bladder wall was irradiated and the light fluence rates were measured with the light source in the center, 1 cm out of the center in the direction of one of the light detectors, and 1 cm out of the center in the opposite direction. Next, the bladder was filled with a solution of 136(5) ml of saline plus 14 ml of Intralipid®-10% (Kabi Pharmacia AB, Sweden), resulting in a scattering coefficient of ≈45 $cm^{-1}$ [12]. Again, the bladder wall was irradiated and the light fluence rates were measured with the light source in- and out of the center as above.

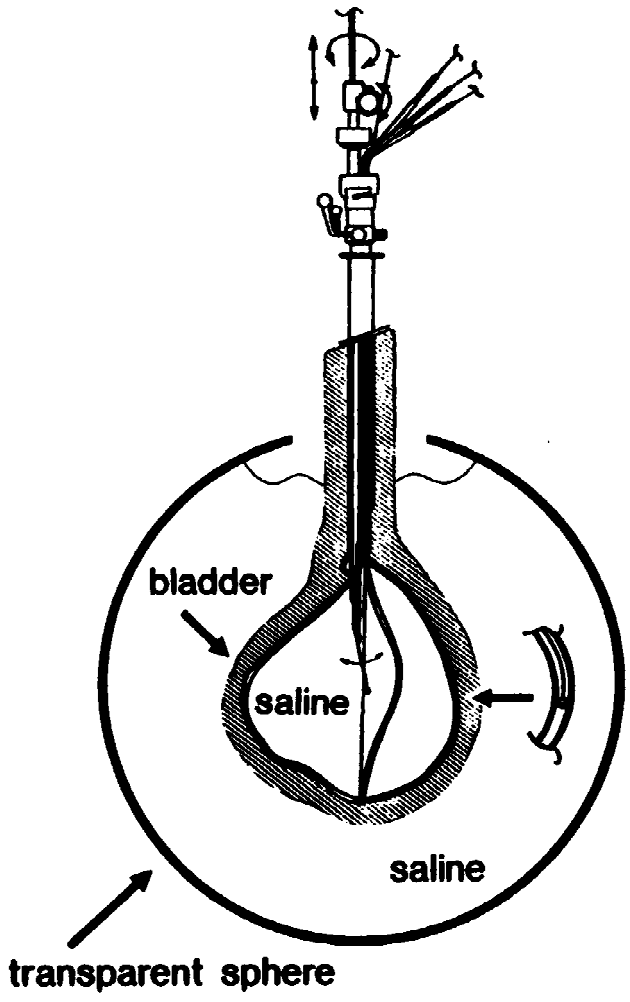


Fig. 1. Experimental setup for the ex vivo WBW light irradiation with a modified cystoscope, which facilitates accurate positioning of the light emitting diffuser and measurement of the light fluence rate at the bladder wall [7].

In vitro phantom experiments were performed on a perfect sphere made of a transparent plastic (diameter 8 cm, volume 250 ml), which was immersed in a glass tank (23 × 21 × 23 cm) filled with a liquid tissue phantom (Fig. 2). The tissue phantom was composed of 6 L of water, 700 ml of Intralipid®-20% as the light scattering component and 55 ml of an Evans Blue solution as the light absorbing component. (The stock suspensions of Intralipid® are available in bottles of 10% and 20%.) This resulted in a tissue phantom with an absorption coefficient ($\mu_a$) of ≈0.5 $cm^{-1}$, a scattering coefficient ($\mu_s$) of ≈100 $cm^{-1}$, and an anisotropy factor (g) of ≈0.77 at 633 nm wavelength [12]. The reduced albedo (a′) of this mixture, $a' =$

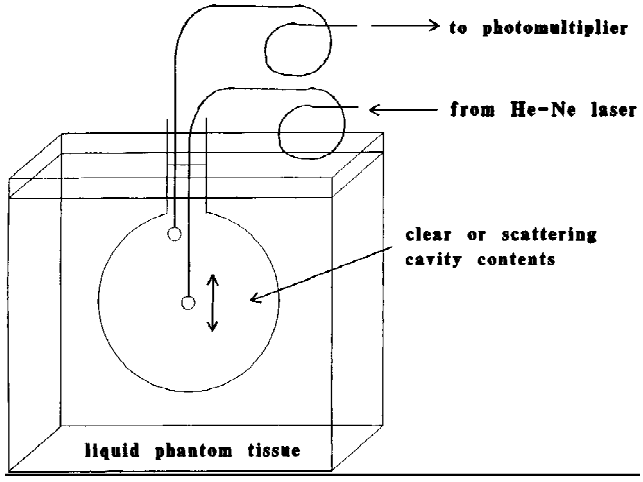


Fig. 2. Experimental set-up for the in vitro bladder phantom optical irradiations. A transparent plastic sphere of 250 ml was immersed in a glass tank (23×21×23 cm) filled with a liquid tissue phantom. The tissue phantom was composed of 6 L of water, 700 ml of Intralipid® –20% and 55 ml of an Evans Blue solution, resulting in $\mu_a \approx 0.5$ cm$^{-1}$, $\mu_s \approx 100$ cm$^{-1}$, and $g \approx 0.77$ at 633 nm wavelength [12]. This mixture will result in a β (see text) of ≈5.3 if the "bladder" is filled with saline [13]. The light emitting and light detecting diffusers can be accurately positioned inside the cavity.

$\mu_s'/(\mu_a + \mu_s') = 0.98$ where $\mu_s'$ is the reduced scattering coefficient, $\mu_s' = \mu_s(1 - g)$, will result in a β of ≈5.3 [13]. Irradiations were performed with 633 nm light from a He-Ne laser and the light fluence rate Φ was measured at the neck of the "bladder" cavity. If the isotropic light source (isotropy < ±15%) was positioned in the center of the cavity, the deviations from the mean fluence rate at the wall were always <5% across the whole "bladder" surface. Calibration of the isotropic light detector (isotropy < ±20%) and the output power was checked before and after the experiments (deviations <3% and <5%, respectively) [11]. First, the "bladder" cavity was filled with 250 ml of saline. The "bladder" wall was irradiated and the light fluences were measured with the light source in the center, 1 cm up- and 1 cm down out of the center. Next, the cavity was filled with a solution of 227 ml of saline plus 23 ml of Intralipid®-10% resulting in a $\mu_s \approx 45$ cm$^{-1}$ [12], which is identical to the $\mu_s$ of the contents in the ex vivo experiment. Again, the wall was irradiated and the light fluences were measured with the light source in- and out of the center as above.

To simulate the ex vivo experiment, the mean in vitro optical properties of pig bladder at 630 nm were used. The $\mu_a$, $\mu_s$, and g of 12 pig bladders had been previously determined [8, 9] using a double integrating sphere setup [14, 15]. The mean refractive index ($n$) was determined in vitro of four pig bladders at 633 nm using a rotating prism [13].

The mean optical properties at ≈630 nm used for the computer simulation of the ex vivo experiment were $\mu_a = 0.6(4)$ cm$^{-1}$, $\mu_s = 186(18)$ cm$^{-1}$, $g = 0.93(2)$, and $n = 1.36(1)$ for the bladder tissue, and $n = 1.33$ for the bladder contents (Table 1). The $\mu_a$, $\mu_s$, and g used for the computer simulation of the in vitro experiment were as the tissue phantom given before and $n = 1.33$ for the tissue phantom as well as for the bladder contents (Table 1). Note that in all computer simulations, the $\mu_a$ of the clear and light scattering medium in the bladder is set to zero.

Computer simulations were performed as described previously [8, 9, 13] using the Monte Carlo (MC) algorithm adapted to a spherical geometry and with the possibility to alter the position of the light source inside the bladder cavity [16]. All simulations were performed with a cavity embedded in a semi-infinite tissue layer. The cavity volume was 150 ml as used in clinical bladder PDT [1,3], which yields a surface area ($A$) of 137 cm$^2$ for the spherical wall. The isotropic point source in the cavity was normalized to an output power ($P$) of 1 W, resulting in $\Phi_{nsl} = P/A = 7.3$ mW cm$^{-2}$ in all simulations. The mean light fluence rate Φ in tissue along the perimeter of the cavity and into the tissue was then determined. Note that in case of light scattering bladder contents $\beta = \Phi/\Phi_{nsl}$ was also calculated with an irradiance of $\Phi_{nsl} = P/A$. The actual irradiance is unknown, but is, of course, much lower due to intravesical scattering and absorption.

## RESULTS

All experimental and simulation results are summarized in Table 1. For central positions of the light source the β values are given, whereas for eccentric light sources the light fluences are given relative to the light fluences with the light source in the center (= β relative to β with the light source in the center).

In the case of the ex vivo experiment, the β values measured should be regarded as lower limits. As the thickness of the bladder wall was rather small (1–2 mm), the contribution of scattered light to the total light fluence was limited to a tissue layer far from (semi-)infinite as was the case in the MC simulations. The ex vivo MC sim-

**TABLE 1. Overviews of Experimental β Values in WBW Optical Irradiations Compared to MC Simulations***

| | In vitro optical parameters | | | | | | | Relative light fluence at the bladder wall | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | bladder tissue | | | | bladder contents ($\mu_a$ = 0) | | | light source in center β | light source 1 cm out of center | |
| | $\mu_a$ ($cm^{-1}$) | $\mu_s$ ($cm_{/1}$) | g | n | $\mu_g$ ($cm^{-1}$) | g | n | | min. relative to cener | max. relative to center |
| Ex vivo pig | — | — | — | — | 0 | — | 1.33 | 5.2(3) | 0.70 | 2.3 |
| experiment | — | — | — | — | ≈45 | ≈0.77 | 1.33 | 5.2(3) | 0.35 | 6.0 |
| Ex vivo MC | 0.6 | 186 | 0.93 | 1.36 | 0 | — | 1.33 | 4.1(1) | 0.55 | 1.9 |
| simulation | 0.6 | 186 | 0.93 | 1.36 | 45 | 0.77 | 1.33 | 3.9(4) | 0.50 | 2.7 |
| In vitro phantom | ≈0.5 | ≈100 | ≈0.77 | 1.33 | 0 | — | 1.33 | 5.3(7) | 0.86 | 1.2 |
| experiment | ≈0.5 | ≈100 | ≈0.77 | 1.33 | ≈45 | ≈0.77 | 1.33 | 19(3) | 0.47 | 2.5 |
| In vitro MC | 0.5 | 100 | 0.77 | 1.33 | 0 | — | 1.33 | 8.6(4) | 0.89 | 1.3 |
| simulation | 0.5 | 100 | 0.77 | 1.33 | 45 | 0.77 | 1.33 | 9.0(6) | 0.49 | 2.3 |

*With the light source in the center of the bladder cavity, β is defined as the measured (or simulated) light fluence rate Φ at the bladder wall divided by the calculated irradiance $\Phi_{nsl}$. With the light source 1 cm out of the center of the bladder cavity, the minimum and maximum light fluences are given relative to the light fluence with the light source in the center. Numbers in parentheses are the standard deviation uncertainties in the last digit(s) of each quoted value.

ulation yielded somewhat lower β values than the mean value of ≈5 encountered in clinical practice, due to a smaller $\mu_s$ and/or a larger $\mu_a$ or g.

In the case of the in vitro experiment with a light scattering medium in the bladder, a large β of 19(3) was measured. This was not due to the position of the light detector near the neck, as comparable values were measured at the opposite side of the cavity at the bottom. This should rather be attributed to the fact that the light detector was immersed in the light scattering bladder contents a couple of millimeters from the tissue phantom, as the thickness of the plastic wall and the diameter of the detector were both ≈1–1.5 mm. It can increase the measured fluence rate significantly, whereas it hardly influences the measured fluence rate in case of a clear medium in the bladder.

All the ex vivo and in vitro experiments and the MC simulations show that for an isotropic light source in a spherical bladder geometry, the clear bladder content gives less deviation from uniform irradiation when the light source is out of the center than in case of scattering bladder content.

In Figure 3, the simulated light fluence rates Φ(R + d) of the in vitro experiment are plotted versus *d,* where *R* is the radius of the bladder cavity, *d* is the depth into the bladder wall, and Φ(R) = Φ. These figures show that for the light scattering cavity contents, the optical penetration depth (δ), defined as the depth where Φ(R + δ) = Φ(R)/e with e the base of the natural logarithm, is reduced from ≈2 mm to ≈1.5 mm. The optical penetration depth also can be estimated from $\delta = \mu_{eff}^{-1}$, where $\mu_{eff} = (3\mu_a\mu_{tr})^{1/2}$ is the effective attenuation coefficient and $\mu_{tr} = \mu_a + \mu_s(1 - g)$ is the transport attenuation coefficient. With $\mu_{eff}$ = 5.9 $cm^{-1}$ for the tissue phantom this yields δ = 1.7 mm, which is in agreement with the MC simulations.

## DISCUSSION

Bladder PDT is sometimes performed with a light scattering medium in the bladder [5]. It is assumed that for all irradiation modalities, i.e., with a flat cut fiber or an isotropic diffuser, the benefit would be a more uniform illumination of the bladder wall. It is evident that when a flat cut fiber is used as a light source, a scattering medium will improve the uniformity of the illumination [17]. Since a whole bladder wall treatment using (fairly) isotropic spherical diffusers is the accepted treatment modality for bladder PDT, the influence of an eccentric isotropic light diffuser on the homogeneity of the light distribution at the bladder wall was investigated at ≈630 nm.

We have shown experimentally and with computer simulations in a spherical bladder geometry that a clear bladder contents gives less deviation from the uniform illumination with an eccentric isotropic light source than a light scattering bladder contents. This phenomenon was demonstrated before by Star et al. [18]. Thus, WBW-PDT with clear, saline bladder contents will be technically more advantageous, as it is easiest to obtain the most uniform light distribution possible.

Also, the optical penetration depth will be

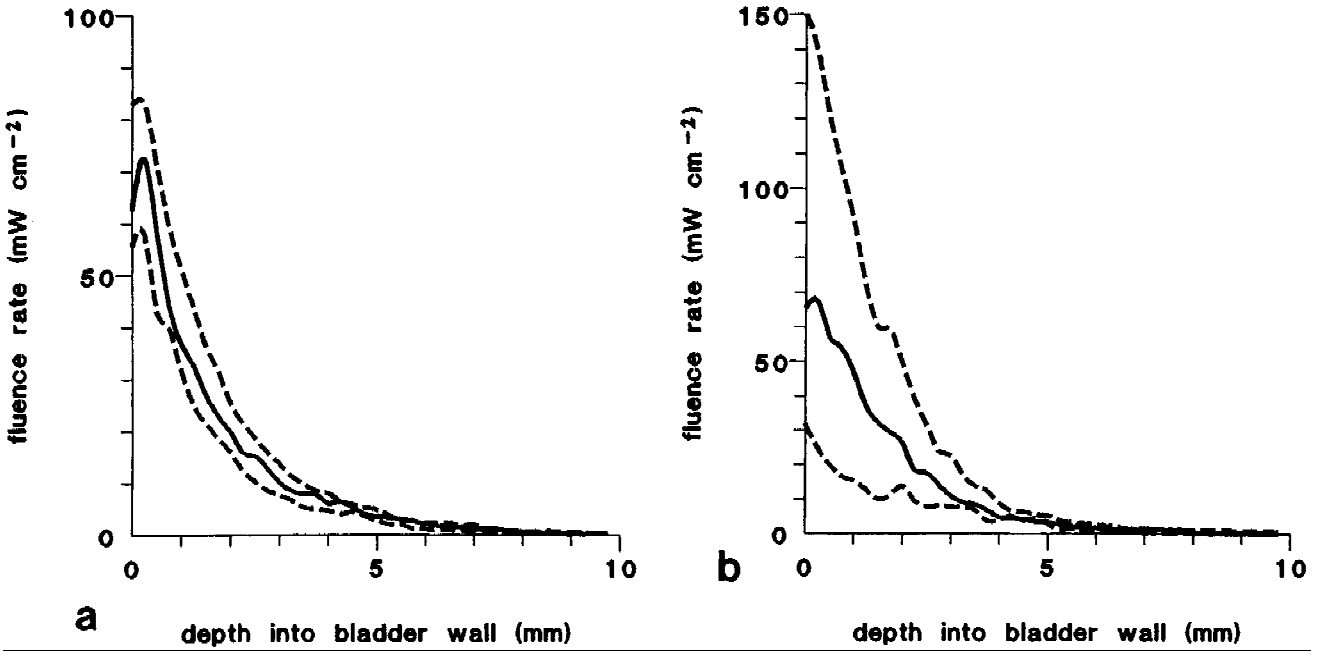


Fig. 3. Plot of simulated light fluence rates versus depth into bladder wall, using the optical properties of the bladder phantom at ≈630 nm wavelength, a cavity volume of 150 ml and a 1 W isotropic light source. At the bladder wall $\Phi_{nsl}$ = 7.3 mW cm$^{-2}$. MC simulations were performed for (**a**) clear and (**b**) light scattering cavity contents, a centred light source (solid lines) and a light source 1 cm out of the centre (dashed lines). The optical penetration depth δ, defined as the depth where $\Phi(R + \delta) = \Phi(R)/e$ with e the base of the natural logarithm, is ≈2 mm for the clear cavity contents and ≈1.5 mm for the light scattering cavity contents.

smaller in case of a light scattering medium in the bladder, as was demonstrated in the MC simulations. This is a result of the steeper reduction of the fluence rate inside the tissue for diffuse incident light [6, 18, 19].

Furthermore, light absorption by urine in the bladder cavity is often inevitable during a clinical procedure. In case of light scattering cavity contents, even the slightest light absorption inside the cavity would lead to a substantial loss of the energy delivered. For instance, MC simulations of the in vitro experiment with cavity contents of $\mu_a$ = 0.01 cm$^{-1}$, $\mu_s$ = 45 cm$^{-1}$, and g = 0.77 ($\mu_{eff} \approx$ 0.56 cm$^{-1}$, $\delta \approx$ 1.8 cm), show that ≈40% of the delivered energy is absorbed in the cavity and β drops from 9.0 to ≈4.5. Note that according to Van Staveren et al. [12], the $\mu_a$ of the Intralipid® –10% suspension used in the bladder may already be 0.014 cm$^{-1}$ ($\mu_{eff} \approx$ 0.66 cm$^{-1}$, $\delta \approx$ 1.5 cm). As the $\mu_a$ encountered in clinical practice may even be much larger, the use of intravesical light scattering media should be out of the question in bladder PDT systems without a closed-off balloon.

It should be noted that the results of the MC simulations have intrinsic uncertainties. As the fluence rate is recorded in (small) boxes in a plane through the center of the bladder cavity, the fluence rate is an evenly distributed value over the entire box area and will be intermediate between the (larger) fluence rate at the bladder surface side and the (smaller) fluence rate at the bladder tissue side. MC calculations would produce higher β values if simulations were performed using a grid with smaller dimensions than used here (250×250 μm). This is markedly true for large β values.

Since the therapeutic ratio in clinical bladder PDT is directly related to the uniformity of the irradiation and the delivered light fluence, and as a relatively small eccentricity of the light source results in large deviations from the mean light fluence rate, optical WBW irradiations in nonspherical bladders should be performed with some kind of in situ light dosimetry.

## CONCLUSION

The use of a light scattering intravesical medium during optical irradiation with an isotropic

light source in clinical PDT of nonspherical bladders is unsuitable to achieve a high and uniform fluence rate at the bladder wall. A higher and more uniform fluence rate is realized by a clear intravesical medium.

## ACKNOWLEDGMENTS

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